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COCAINE ABUSERS SHOW A BLUNTED RESPONSE TO ALCOHOL INTOXICATION IN LIMBIC BRAIN REGIONS

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Abstract: Cocaine and alcohol are frequently used simultaneously and this combination is associated with enhanced toxicity. We recently showed that active cocaine abusers have a markedly enhanced sensitivity to benzodiazepines. Because both benzodiazepines and alcohol facilitate GABAergic neurotransmission we questioned whether cocaine abusers would also have an enhanced sensitivity to alcohol that could contribute to the toxicity. In this study we compared the effects of alcohol (0.75 g/kg) on regional brain glucose metabolism between cocaine abusers (n=9) and controls (n=10) using PET and FDG. Alcohol significantly decreased whole brain metabolism and this effect was greater in controls (26 ±6%) than in abusers (17 ±10 %) even though they had equivalent levels of alcohol in plasma. Analysis of the regional measures showed that cocaine abusers had a blunted response to alcohol in limbic regions, cingulate gyrus, medial frontal and orbitofrontal cortices. Conclusions: The blunted response to alcohol in cocaine abusers contrasts with their enhanced sensitivity to benzodiazepines suggesting that targets other than GABA-benzodiazepine receptors are involved in the blunted sensitivity to alcohol and that the toxicity from combined cocaine-alcohol use is not due to an enhanced sensitivity to alcohol in cocaine abusers. The blunted response to alcohol in limbic regions and in cortical regions connected to limbic areas could result from a decreased sensitivity of reward circuits in cocaine abusers. © 2000 Elsevier Science Inc.

Key Words: drug addiction, reward, brain glucose metabolism, positron emission tomography, neurotoxicity

Introduction

The simultaneous use of cocaine and alcohol is one of the most frequent patterns of combined drug use (1). Alcohol is combined with cocaine to reduce the dysphoria experienced after a cocaine binge (crash), to calm down after a binge and/or to prolong the euphoria. Epidemiological studies have shown that the combined use of cocaine and alcohol may be synergistically toxic (2). It has been estimated that the combined use of cocaine and alcohol results in a marked increase in the risk of sudden death (3).

Using positron emission tomography (PET) and 2-deoxy-2[^{18}F]fluoro-D-glucose (FDG) we have shown that active cocaine abusers have an increased sensitivity to the behavioral and regional brain

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metabolic effects of benzodiazepines (4), which are drugs that enhance GABA neurotransmission (5). Because alcohol also facilitates GABA neurotransmission (5) we questioned whether cocaine abusers would also have an enhanced sensitivity to alcohol. This is relevant since if they do it could contribute to the enhanced morbidity and mortality reported when cocaine abusers combine cocaine with alcohol. This study compares the behavioral and the regional brain metabolic responses to acute alcohol administration between active cocaine abusers and controls using PET and FDG.

Methods

Subjects: Nine active cocaine abusers (41 ±8 years old) were recruited by advertisement. Subjects met DSM IV diagnostic criteria for active cocaine dependence, used cocaine continuously for at least the prior 6 months with claimed use of at least "three grams" a week and used cocaine as smoked free-base and/or intravenously. Subjects were excluded if they had current or past psychiatric disease (other than cocaine dependence) or neurological disease, history of head trauma with loss of consciousness, current medical illness, drug dependence (other than cocaine, nicotine or caffeine) and more than moderate (12 ounces/week) use of alcohol. Controls were 10 healthy volunteers (36 ±5 years of age). Exclusion criteria were otherwise the same as those for the cocaine abusers. None of the subjects was taking medication at the time of the study. Evaluation of subjects was performed consistently by the same clinician (GJW). As part of the evaluation procedure, subjects had a physical, psychiatric and neurologic examination. Routine laboratory tests were performed as well as a random urine test to exclude the use of psychoactive drugs other than cocaine in the abusing group. Subjects were instructed to refrain from drinking alcohol the week prior to the PET scan. Cigarettes, food and beverages were discontinued at least 4 hours prior to the study. Table 1 provides demographic characteristics of the subjects. Written informed consent was obtained for all subjects after procedures had been fully explained.

TABLE 1

Demographic Characteristics of Subjects.

	Comparison Group (N=10)	Cocaine Abusing Group (N=9)
Age	41 ±8	36 ±5
Education	15 ±2	13 ±2
Years of cocaine use	0	15 ±7
Cocaine use (grams/week)	0	6.5 ±5
Days without cocaine	Not applicable	2.5 ±2
Smokers	2	7
Alcohol (beers/day)	1.4 ±2	2 ±2

Subjects had comparable demographic characteristics except for their histories of cocaine abuse and for a higher frequency of smokers in the cocaine abuser than in the control group.

Scans: Subjects were scanned using a Siemens HR+ resolution 4.5 x 4.5 x 4.5 mm FWHM, 63 slices each 2.4 mm thick, 3D mode) as described (6). Briefly, emission scans were taken 35 minutes following injection of 4-6 mCi of FDG for a total of 20 minutes. Arterialized blood was obtained to measure plasma concentration of F-18, glucose, PO_2, pCO_2 and plasma alcohol (7). Each subject underwent two PET FDG scans obtained within 1 week of each other. For one scan subjects drank a placebo (100 ml of diet noncaffeinated soda) and for the other they drank alcohol (0.75gm/kg mixed with 100 ml of diet noncaffeinated soda) over a 40 minutes period. FDG was injected 40-50 minutes after alcohol or placebo. Subjects were blind to the drug received and were scanned with their eyes open ears unplugged in a dimly lit room with noise kept to a minimum.

Behavioral measures: Behavioral effects for intoxication, high, desire for alcohol and sleepiness were measured using analog self rating scales (0-10) prior to and at 20, 40, 55, 80 and 140 minutes after placebo or alcohol. Before placebo or alcohol and at 55 and 140 minutes after their administration subjects were tested with the Stroop test, the Word Association test, the Symbol Digit Modality test (SDMT), and arithmetic calculations.

Image Analysis: Regions were selected using a template based on the Talairach & Tournoux's atlas that identified 40 brain areas, each of which was obtained by averaging left and right measures over at least 3 sequential planes (8). To limit the number of statistical tests the measures were combined into 12 large regions.

Statistical Analysis Differences in the regional metabolic responses to alcohol between the groups were tested using the percent change in metabolic activity ((Placebo – Alcohol/Placebo) x 100)) with one factor (diagnosis) repeated (regions) measures ANOVA. Post hoc t tests were then performed to assess the brain regions, where these differences were significant. Pearson product moment correlation analysis was used to assess the relationship between changes in metabolism and alcohol-induced behavioral and cognitive changes (Baseline – Alcohol). Differences in alcohol-induced behavioral and cognitive changes and differences in plasma alcohol concentration between the groups were tested with ANOVA. Significance for repeated tests was set at $p < 0.01$.

Results

Plasma alcohol concentrations did not differ between groups and corresponded in the controls and the cocaine abusers respectively to 34 ±21 and 45 ±25 ng/ml at 20 minutes, 100 ±35 ng/ml and 102 ±41 at 40 minutes, 111 ±35 ng/ml and 135 ±59 at 55 minutes, 103 ±22 ng/ml and 113 ±33 at 80 minutes, 96 ±16 ng/ml and 102 ±25 at 100 minutes and 89 ± 11 and 87 ±23 ng/ml at 130 minutes.

Alcohol induced significant increases in self-reports of intoxication and high and though these effects tended to be higher in abusers than in controls these differences did not reach significance. Baseline measures for cognitive performance differed between the groups; abusers performed worse than controls in the Stoops, SDMT and arithmetic calculations (Table 2). Alcohol disrupted cognitive performance and these effects did not differ between the groups (Table 2).

TABLE 2
Behavioral and Cognitive Measures Obtained after Placebo and Alcohol.

	Controls		Cocaine Abusers		ANOVA	
TEST	Baseline	Alcohol	Baseline	Alcohol	Group *p*	Drug *p*
Desire Alcohol	0	0	1 ±2	1 ±2	NS	NS
Intoxication	0	5 ±2	0	7 ±3	NS	0.0001
High	0	4 ±2	0	7 ±3	NS	0.0001
Sleepiness	1±1	2 ±3	3 ±2	2 ±3	NS	NS
Stroop-Read	97 ±24	88 ±11	84 ±20	67 ±19	NS	0.003
Stroop-Color	78 ±12	68 ±8	63 ±13	54 ±16	0.05	0.0005
Stroop-Int	55 ±12	45 ±7	35 ±10	34 ±10	0.0005	0.05
SDMT	53 ±1	42 ± 11	43 ±6	35 ±7	0.03	0.0009
WA	16 ±5	11 ±3	12 ±4	7 ±2	NS	0.0001
Calculation	13 ±2	12 ±2	10 ±2	9 ±1	0.02	0.006

Self rating (0-10) for drug effects (desire of alcohol, intoxication, high and sleepiness) averaged for measures obtained at 40 and 55 minutes after alcohol. Cognitive tests involved the Stroop (Read, Color and interference (Int)), symbol digit modality test (SDMT), word association (WA) and arithmetic calculations. The drug by group interaction effect was not significant.

The baseline metabolic measures did not differ between controls and abusers (Table 3).

TABLE 3
Baseline Regional Brain Metabolic Measures (μmol/100g/min)

	Controls	Cocaine Abusers
Frontal Lateral	42.1 ±7	40.6 ±11
Frontal Medial	37.5 ±6	36.7 ±10
Cingulate Gyrus	36.7 ±7	35.4 ±9
Orbitofrontal Cortex	37.3 ±8	35.8 ±9
Parietal Cortex	38.1 ±6	36.6 ±9
Temporal Cortex	32.8 ±5	32.6 ±8
Occipital Cortex	45.0 ±8	43.6 ±11
Thalamus	36.7 ±7	35.6 11
Striatum	37.3 ±7	39.6 ±10
Insula	36.2 ±7	36.2 ±10
Limbic Region	24.7 ±4	24.2 ±7
Cerebellum	28.3 ±4	28.4 ±7

Alcohol decreased global metabolism (average activity in 40 regions) and the effects were smaller in abusers (17 ±10 %) than controls (26 ±6%) ($F = 5.6$, df 1,18 $p < 0.05$) (Figure 1).

Fig. 1
Brain metabolic images at the level of the centrum semiovale (left) and of the orbitofrontal cortex (right) for a control and for a cocaine abuser after placebo and after alcohol. Alcohol decreased metabolism and the changes were larger in the control than in the cocaine abuser.

The ANOVA on the regional measures (% change from placebo) showed a significant difference between groups ($F = 6$, df 1,17 $p < 0.05$), between regions ($F = 4.8$, df 11. $p < 0.0001$) and between the group by region interaction ($F = 1.8$, df 11,187 $p < 0.05$). The significant group effect indicates that alcohol-induced changes differed between groups and was lower in abusers than controls (Figure 2). The significant region effect indicates that alcohol effects differed across brain regions; it was largest in occipital cortex (28 ±11%) and cerebellum (28 ±13%) and was lowest in striatum (19 ±13%) (Figure 2). The significant group by region interaction effect indicates that alcohol-induced differences between the groups differed across brain regions. Post hoc t tests showed that differences between the groups were significant in the cingulate gyrus (t =

2.9, df 17. $P < 0.01$), orbitofrontal ($t = 3$, df, 17 $p < 0.01$), and medial frontal cortices ($t = 3$, df, 17 $p < 0.01$) and in the limbic region (comprised of amygdala, hippocampus and parahippocampus) ($t = 2.9$, df, 17 $p < 0.01$) (Figure 2). There were no significant correlations between metabolic changes and the behavioral and cognitive changes induced by alcohol.

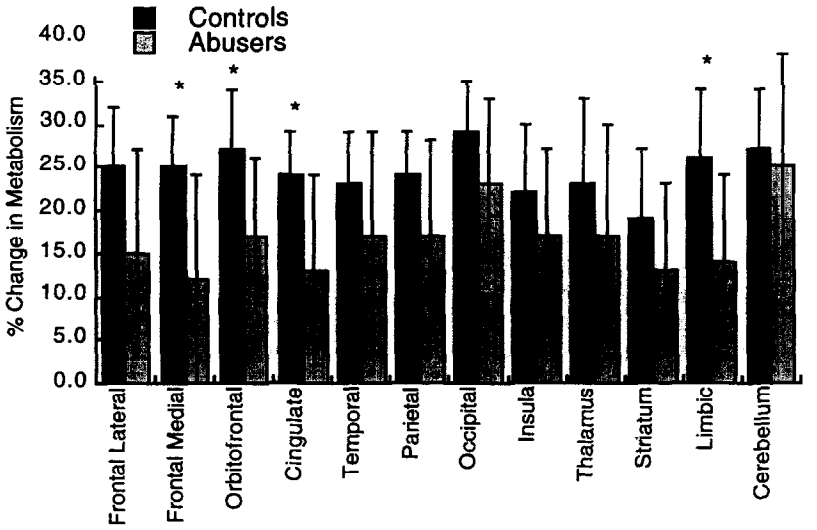

Fig. 2
Regional changes in metabolism induced by alcohol in controls and in cocaine abusers. Alcohol-induced decrements in regional brain glucose metabolism were significantly larger in controls than in cocaine abusers. * $p < 0.01$.

Discussion

This study documents a decreased sensitivity to alcohol in active cocaine abusers as assessed by the blunted reduction of brain glucose metabolism. These results contrast with our previous findings showing an enhanced metabolic response to the benzodiazepine drug lorazepam in active cocaine abusers. This most likely reflects the fact that the molecular targets mediating the effects of lorazepam and alcohol on regional brain metabolism differ. For lorazepam its effects are predominantly mediated by its activation of benzodiazepine receptors, which are part of the GABAA receptor complex (9), since treatment with the benzodiazepine antagonist flumazenil reverses the metabolic changes (10). Alcohol's effects on metabolism are likely to involve not only facilitation of GABA neurotransmission but also activation and inhibition of other receptors (dopamine, serotonin, GABA, opiates, glutamate (11)). Though a similar distribution in brain has been reported for GABAA receptors sensitive to alcohol and to benzodiazepines (12) these receptors have different subunit composition and different pharmacological characteristics (5). In this respect it is interesting to note that the behavioral effects seen with lorazepam differed to those seen during alcohol intoxication. Lorazepam induced significant increases in self-reports of sleepiness in proportion to the decrements in metabolic activity in thalamus, which is a brain region that was more sensitive to lorazepam than to alcohol, whereas alcohol did not induce sleepiness and while alcohol induced increases in self ratings of high and intoxication lorazepam did not. Hence the marked decreases in regional brain metabolism seen in the cocaine abusers after lorazepam may have been driven by the enhanced sensitivity in these subjects to the sedative effects of this drug. However, this study can not rule out the possibility that differences in the responses obtained in this study with alcohol and in the study with lorazepam may reflect in part the differences in the placebo condition, which for intravenous lorazepam may have led to better

blinding than for alcohol for which an adequate placebo is difficult. Thus the expectations levels prior to drug administration may have affected the drug responses differently for the alcohol than the lorazepam study and expectation effects may differ between controls and abusers.

The blunted regional responses in the cocaine abusers, which were confined to brain limbic regions and to cortical regions closely connected with them, could reflect dysfunction of brain reward circuits involved with addiction (13). Abnormalities in the orbitofrontal cortex and cingulate gyrus have been reported in other drug addictions including alcoholism and have been implicated in the compulsive drug administration and the loss of control seen in addicted subjects (14). Dysfunction of the orbitofrontal cortex and the cingulate gyrus, which are brain regions involved in the regulation of "drive" (15), could also contribute to the process of addiction by affecting motivation. Recent imaging studies have implicated limbic brain regions (amygdala and hippocampus) in drug craving, (16).

Because brain glucose metabolism mainly reflects activity in terminal regions (17) the differences in the metabolic changes induced by alcohol most likely reflect differences in sensitivity of projecting neurons. Frontal and limbic regions receive projections from DA and serotonin cells and are sensitive to alcohol's effects (18). Thus, one could speculate that the decreased metabolic response to alcohol in cocaine abusers could reflect decreased sensitivity of DA cells (VTA) and/or serotonin cells (dorsal raphe). In fact decreased sensitivity of DA cells has been documented in detoxified cocaine addicted subjects (19). Moreover, the reductions in DA D2 receptors in detoxified cocaine abusers have been associated with changes in metabolic activity in cingulate gyrus, middle frontal gyrus and orbitofrontal cortex (20). On the other hand blunted responses in these brain regions have also been reported after serotonergic stimulation in alcoholic subjects (21). However, alcohol also affects other neurotransmitters and hence further studies are necessary to determine the neurotransmitters responsible for the abnormal responses to alcohol in the cocaine abusers.

Cocaine abusers performed worse than the control in the Stroop and the SDMT. The poorer performance could reflect in part disruption of DA activity since DA modulates the activity of the brain regions involved in the execution of these tests (22) and cocaine abusers have decreased brain DA activity (19).

Though not significant the responses of the cocaine abusers to self-reports of high and intoxication were higher than those in the controls and it is possible that a larger sample may have revealed a significant effect. This seemingly paradoxical pattern in the cocaine abusers of a blunted response to the metabolic effects of alcohol in limbic brain regions but a tendency to a higher sensitivity to its reinforcing effects suggests that the reinforcing effects of alcohol are not mediated by the decrease in metabolic activity in these limbic brain regions. This is also corroborated by the failure to detect a correlation between alcohol's effects in regional brain metabolism and its behavioral effects. In alcoholic subjects we had reported the opposite "paradoxical pattern" an enhanced metabolic response to alcohol but a blunted response to the behavioral effects of ethanol (23). The reason for this seemingly paradoxical dissociation between the behavioral and the metabolic effects of alcohol is unclear but could reflect in part direct effects of alcohol on cell energy metabolism (24). However, failure to observe a significant correlation between metabolic and behavioral changes could also reflect the relatively poor temporal resolution of the FDG method, which limits its sensitivity for detecting activation patterns associated with behaviors that vary over the 20-25 minutes period of FDG uptake.

In summary this study documents a blunted sensitivity to alcohol in cocaine abusing subjects that was most accentuated in limbic and in frontal regions connected with limbic areas. This blunted response in cocaine abusers contrasts with the enhanced sensitivity to lorazepam suggesting that mechanisms other than GABA are likely to be involved in these differences and that the toxicity from the combined use of cocaine and alcohol reported in cocaine abusers is not due to an enhanced sensitivity to alcohol in these subjects. Further studies are required to determine the molecular targets involved in these blunted responses and to assess whether these changes will recover with detoxification.

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